Environmental Health Perspectives
Vol. 86, pp. 3–5, 1990

Symposium Overview: Toxicology, Carcinogenesis, and Human Health Aspects of 1,3-Butadiene

by Ronald L. Melnick,* J. E. Huff,* Michael G. Bird,† and John F. Acquavella†

1,3-Butadiene (CH_2=CH–CH=CH_2), a high-volume, colorless gas, used mainly in the production of synthetic rubber, has long been considered to have low and noncumulative toxicologic potential in animals and humans. In fact, the current standard of 1000 ppm, promulgated by the Occupational Safety and Health Administration (OSHA) as an 8-hr, time-weighted average (TWA) workroom exposure concentration, was aimed at preventing irritation to the eyes and upper respiratory tract of exposed workers. However, results of long-term inhalation studies conducted by the National Toxicology Program and by the International Institute of Synthetic Rubber Producers showed that 1,3-butadiene is carcinogenic in mice and rats. These findings raised greater concerns of potential risk for humans exposed to this chemical. In 1984, the American Conference of Governmental Industrial Hygienists reduced their recommended threshold limit value-TWA for 1,3-butadiene from 1000 to 10 ppm. In February 1984, the National Institute for Occupational Safety and Health (NIOSH) issued a hazard alert indicating that 1,3-butadiene should be regarded as a potential occupational carcinogen (Current Intelligence Bulletin 41). OSHA is evaluating the current workplace standard for this chemical.

To provide an open forum to evaluate the current state of knowledge on the toxicology, carcinogenesis, and human health aspects of 1,3-butadiene and to discuss ongoing studies or those being planned, an international symposium on 1,3-butadiene was held at the National Institute of Environmental Health Sciences in Research Triangle Park, North Carolina, on April 12 and 13, 1988. Scientists from government, industry, and academia, who are actively examining various health-related aspects of 1,3-butadiene, presented results of their new or updated studies and participated in general discussions aimed at furthering our understanding of the scientific facts, and the key issues that will have an impact on regulatory decisions aimed at protecting the health of the public and of workers occupationally exposed to 1,3-butadiene.

This meeting was sponsored by government, industry, and union groups: the National Institute of Environmental Health Sciences (NIEHS), the International Institute of Synthetic Rubber Producers (IISRP), the National Institute for Occupational Safety and Health (NIOSH), the Occupational Safety and Health Administration (OSHA), the Environmental Protection Agency (EPA), the Industrial Union Department (IUD), and the Chemical Manufacturers Association (CMA). Approximately 120 people participated in the meeting, with participants from Canada, Federal Republic of Germany, Great Britain, Italy, Mexico, Netherlands, and the United States.

The two-day symposium was divided into seven sessions: 1) "Industrial use and occupational exposure to 1,3-butadiene," chaired by L. Beliczky, United Rubber Workers Union, Akron, OH; 2) "Carcinogenicity studies of 1,3-butadiene in rats and mice," chaired by J. Huff, NIEHS, Research Triangle Park, NC; 3) "Mechanistic and pharmacokinetic studies of 1,3-butadiene in rats and mice," chaired by M. Wooder, Shell International Petroleum, The Hague, Netherlands; 4) "Genetic and developmental toxicology studies of 1,3-butadiene," chaired by E. Loeser, Bayer AG, West Germany; 5) "Toxicology studies of isoprene (2-methyl-1,3-butadiene)," chaired by R. Scala, Exxon Biomedical Sciences, East Millstone, NJ; 6) "Epidemiology studies of 1,3-butadiene," chaired by D. Hoel, NIEHS, Research Triangle Park, NC; and 7) "Risk assessment of 1,3-butadiene," chaired by J. D. Millar, NIOSH, Centers for Disease Control, Atlanta,

*National Institute of Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC 27709.

†Exxon Biomedical Sciences, Inc., Mettlers Rd., CN 2350, East Millstone, NJ 08875-2350.

Address reprint requests to R. L. Melnick, National Institute of Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC 27709.

GA. A brief summary and overview of the data and key findings presented at the symposium are given below. More details and extended discussions can be obtained from the following 25 individual papers that comprise these proceedings.

The annual production of 1,3-butadiene is about 3 billion pounds in the United States and approximately 12 billion pounds worldwide (N. L. Morrow, Exxon Chemical Co.). Annual atmospheric emissions of 1,3-butadiene from production or polymer manufacturing plants is approximately 10 million pounds, most of which is attributable to equipment leaks (J. A. Mullins, Shell Oil Co.). Occupational exposure to 1,3-butadiene in monomer production or from polymer manufacturing plants is generally less than 20 ppm; however, excursions in certain jobs resulted in exposures as high as 375 ppm (J. M. Fajen, NIOSH).

In laboratory animal studies, 1,3-butadiene produced neoplasms at multiple organ sites in Sprague-Dawley rats (pancreas, uterus, Zymbal gland, mammary gland, thyroid, and testis) (P. E. Owen, Hazleton, UK) and $B6C3F_1$ mice (lymphoma, heart, forestomach, lung, liver, mammary gland, and ovary) (R. L. Melnick, NIEHS; R. A. Miller, Battelle Pacific Northwest Labs) at exposure levels of 1000 ppm for the rat and 625 ppm for the mouse. In other experiments just completed, multiple organ neoplasia and gonadal atrophy were observed in mice exposed to concentrations as low as 62.5 ppm of 1,3-butadiene for 65 weeks; data for the 2-year exposures are currently being evaluated and will be made available later this year.

Research aimed at explaining the species differences in organ sites of butadiene-induced carcinogenicity has focused on the potential influence of an endogenous retrovirus in $B6C3F_1$ mice (R. D. Irons, Chemical Industry Institute of Toxicology) and on pharmacokinetic considerations (A. R. Dahl, Lovelace Biomedical and Environmental Research Institute; R. J. Laib, Institut für Arbeitsphysiologie und der Universitat Dortmund). A retrovirus involvement was suggested since the incidence of thymic lymphomas was induced to a lesser extent in NIH Swiss mice than in $B6C3F_1$ mice that were exposed to 1250 ppm butadiene for 1 year, and the endogenous ecotropic retrovirus recovered from tissues of $B6C3F_1$ mice was not expressed in exposed NIH Swiss mice. Inhalation pharmacokinetic studies have shown that butadiene is metabolized more rapidly by mice than rats and that reactive monoepoxide and diepoxide intermediates were produced in both species. DNA and hemoglobin adducts have been detected in rats and mice exposed to radiolabeled butadiene. Hemoglobin adduct measurements may be useful in monitoring workplace exposures to butadiene. 1,3-Butadiene was genotoxic to mouse but not rat bone marrow cells (M. D. Shelby, NIEHS; G. T. Arce, E. I. du Pont de Nemours & Co.). This gas did not induce malformations in rats or mice; however, developmental toxicity in mice was indicated because of the decrease in fetal weight of male mice where the dams were exposed to 40 ppm or higher (R. E. Morrissey, NIEHS).

Complementary toxicologic studies on isoprene, the 2-methyl analog of 1,3-butadiene, are important because of the close structural similarities between these two chemicals. Isoprene, used predominantly in the manufacture of synthetic elastomers, is also genotoxic to bone marrow cells of mice (M. D. Shelby, NIEHS). Isoprene may be metabolized to a reactive and mutagenic diepoxide intermediate (P. G. Gervasi, Instituto di Mutagenesi e Differenziamento) and produces nonneoplastic lesions in the testis, nasal cavity, and forestomach that are similar to those caused by 1,3-butadiene (R. L. Melnick, NIEHS). The rate of metabolism of isoprene appears to be greater in mice than in rats (H. Peter, Institut für Arbeitsphysiologie und der Universitat Dortmund). Further studies are in progress to determine the effects of long-term exposure to isoprene and to compare these results with those found for 1,3-butadiene.

A most important element of the symposium was the update of the three epidemiological cohort mortality studies of workers exposed to 1,3-butadiene (R. A. Lemen, NIOSH; B. J. Divine, Texaco, Inc.; G. Matanoski, Johns Hopkins University). In all three studies, the rates of overall worker mortality as well as mortality for all cancers were lower than those of the general population. However, the finding of excess mortalities from lymphatic and hematopoietic cancers among subgroups of workers occupationally exposed to 1,3-butadiene (e.g., standardized mortality ratios were 500% for lymphopoietic cancers and 660% for leukemia in black production workers) indicates that there is now evidence for the carcinogenicity of butadiene in humans (G. Matanoski, Johns Hopkins University; P. J. Landrigan, Mount Sinai School of Medicine). Conversely, another reported that the evidence for human carcinogenicity is inadequate (M. G. Ott, A. D. Little, Inc.). Available data prior to this meeting did not provide evidence of carcinogenicity of butadiene in humans. As with most epidemiologic studies, these studies lack adequate quantitative exposure data. A case control study of the styrene-butadiene rubber industry is in progress to further evaluate the possible relationship between butadiene exposure and lymphopoietic cancer in humans (J. F. Acquavella, Exxon Biomedical Sciences). The risk assessments for 1,3-butadiene, based on inhalation studies in rats and mice, demonstrate that there is significant predicted risk associated with the occupational exposure to 100 ppm butadiene over a working lifetme (E. A. Grossman, OSHA;) or with air exposure for populations living near industrial sources of butadiene emissions (I. L. Cote, EPA).

Further experimental research on 1,3-butadiene is needed to elucidate the mechanism of 1,3-butadiene-induced carcinogenicity, to resolve further the possible effect of a retrovirus in this process, and to relate species differences in target concentrations of reactive metabolites to differences in organ sites of neoplasia. Alternative metabolic pathways, including those for detoxification, should also be explored further (M. G. Bird,

Exxon Biomedical Sciences). Future work in epidemiology should include updates of the existing studies and quantitative measurements to assess more fully the association between mortality outcome and exposure to 1,3-butadiene (M. G. Ott, Arthur D. Little, Inc.). The additional research on 1,3-butadiene will be helpful in clarifying the carcinogenic relationship of this chemical between animals and humans.

For the success of this symposium on 1,3-butadiene, special appreciation is extended to David Rall, Director, NIEHS; William Tessmer, Managing Director, IISRP; Symposium Organizers (R. L. Melnick, NIEHS and M. G. Bird, Exxon Biomedical Sciences); Session Chairs (L. Beliczky, J. Huff, M. Wooder, E. Loeser, R. Scala, D. Hoel, and J. D. Millar); all of the speakers; the attendees; and the cosponsors.